

Cancel claims 2, 3, 5, 6, 11, 12, 14 and 15 without prejudice or disclaimer.

**REMARKS**

In response to the prior final Official Action dated July 30, 1997, in which the Examiner withdrew the finality of the prior Action and issued a new final Action, applicants hand-carried an Amendment to the Group on October 24, 1997. In order to maintain the pendency of the application, a Notice of Appeal was filed on December 31, 1997. On April 2, 1998, the Examiner issued a new final Action which again withdrew the finality of the previous Action and set forth new rejections over certain prior art combinations and provided an extensive discussion interpreting applicant's invention, the evidence that has been made of record and the teachings of the prior art.

By the present response, independent claims 1 and 10 have been amended to relate to only fentanyl salts and the concentration of fentanyl salts has been revised to reflect more clearly the level above which the iontophoretic flux of the drug is dependent on concentration as illustrated in the present application, particularly Figure 2. This latter revision is also reflected in the amendments to claims 4 and 13. In view of the amendments to claims 1 and 10, claims 2, 3, 5, 6, 11, 12, 14 and 15 have been canceled without prejudice or disclaimer. Since the concentration now recited in claims 1 and 10 was formerly recited in original dependent claims and is in response to the point raised on page 4 of the Action and since the number of claims at issue has been substantially reduced, it is clear that the amendments to the claims are proper and should be entered.

In the Official Action, the Examiner has set forth several grounds of rejection over the prior art. More specifically, the Examiner has maintained the rejection based on Phipps et al, U.S. Patent No. 5,423,739, and Phipps et al, U.S. Patent No. 5,125,894, essentially taking the position that since the art makes the general statement that at a constant current, the rate of drug is independent of drug concentration in the active electrode provided that the concentration is at least above a threshold level, it would be obvious to determine what the concentration is for any drug and for fentanyl in particular. In stating this position, the Examiner has noted that he has changed his position with regard to his characterization that the former claims related to the linear region of operation and has questioned a number of the arguments made in the prior response and the explanation provided by Dr. Phipps in his previous Declaration Under 37 C.F.R. §1.132.

As explained above, the claims have been amended to more clearly recite the linear region of operation in response to the new point raised in the Official Action (which again demonstrates the propriety of the present response). With regard to certain of the other points raised in the Action, provided herewith in Appendix A is a further Declaration Under 37 C.F.R. §1.132 by Dr. Phipps which addresses certain of the points posed by the Examiner and in Appendix B are two literature articles. The literature articles have been submitted in response to the position by the Examiner on pages 8 and 9 of the Action that overdosing by passive flux is not a problem in the art. The literature articles (which are not prior art against the present application) clearly show that overdosing with passive delivery of fentanyl is a substantial concern in the art and that there is further a substantial

concern of possible abuse or misuse of used patches, just as Dr. Phipps stated in his previous Declaration.

With respect to a number of criticisms made by the Examiner concerning other points made by Dr. Phipps in his previous Declaration, the further Declaration by Dr. Phipps addresses certain of the arguments made by the Examiner. For instance, Dr. Phipps has explained that the reason why he did not explain the one sentence statement in the '894 patent is because it was based on the Padmanabhan article and that therefore a discussion of the article was more in order. Turning to the more substantive aspect of the Examiner's arguments, Dr. Phipps has discussed that the Examiner's position is too short sighted. That is, the Examiner has considered the general statement in the '894 patent and drawn the conclusion that the determination of the threshold level for any drug, including fentanyl, is obvious without giving further consideration as to what the art teaches is the "threshold level". It is here that Dr. Phipps has further clarified that the Padmanabhan article teaches that since the mobility of the ions in the solution is much greater than the mobility of the ions through the skin, it is the transport number through the skin and not the concentration in the donor reservoir that is the limiting factor. It is for this reason that the Padmanabhan article indicates extremely low concentrations of hydromorphone down to 1 millimolar can still provide steady state delivery. The '894 patent supports this understanding by setting forth values of hydromorphone concentrations that illustrate constant values down to 10 millimolar concentration.

As further noted by Dr. Phipps, the Kasting and Keister article supports the conclusion that the understanding in the art is that "threshold level" is very low and well below the value defined in the claims of record. Such teachings in the art cannot be ~~dismissed~~ dismissed in view of a line of decisions illustrative of which is In re Dow Chemical, 5 USPQ2d 1529 (Fed. Cir. 1988) where the court stated in reversing a prior art rejection:

In determining whether such a suggestion can fairly be gleaned from the prior art, the full field of the invention must be considered; for the person of ordinary skill is charged with knowledge of the entire body of technological literature, including that which might lead away from the claimed invention... Evidence that supports, rather than negates, patentability must be fairly considered. (at page 1532)

In this specific situation, one also cannot lose sight of the fact that fentanyl is such a potent drug that there is a further reason why one would seek to maintain the concentration of the drug at a low level. In this regard, while the Examiner is correct that there is a difference between concentration and amount, there is a greater likelihood of potential danger if the concentration is high since passive flux in large part depends on concentration differences. It is also true that for a given reservoir volume, the amount of residual fentanyl would be larger for higher concentrations. Thus, the risk of fentanyl abuse is greater for formulations with higher fentanyl concentrations present at the end of treatment. Accordingly, based on the conventional wisdom in the art that the "threshold level" of drug concentration in the reservoir for constant flux is low and armed with the knowledge of the potency of fentanyl, one of ordinary skill in the art would not seek to use the surprising high concentrations defined in the claims of record, absent improper reliance on applicant's own specification.

Turning to the Examiner's reliance on "extraneous ions" as a reason why the present invention is not surprising, Dr. Phipps has noted that the Examiner has seemingly failed to appreciate the role of extraneous ions on the threshold concentration concept. Dr. Phipps has explained that the Examiner incorrectly asserts that; (a) the presence of extraneous ions like  $\text{Na}^+$  and  $\text{K}^+$  in a formulation diminishes the relevance of the Kasting model cited in my previous Declaration; and, (b) that the reason that a higher threshold is observed for some drugs may be due to the extraneous ion concentrations in the formulation employed. Dr. Phipps has stated in making these assertions, the Examiner is assuming that the extraneous ions, if present at the beginning of treatment are still present at the end of treatment. In fact, because small excipient ions (like  $\text{Na}^+$  and  $\text{K}^+$ ) are much more mobile in the solution and skin than the fentanyl ions and are typically present in an amount less than the drug ions, they are substantially depleted during the first part of treatment. Therefore, Dr. Phipps has concluded that the Kasting model is an important and fully appropriate consideration of the state of the art at the time of his invention and, contrary to the assertion of the Examiner, the Kasting model teaches away from his invention, even when extraneous ions are initially present, since it theoretically predicts that no threshold in concentration should exist, that is, that at constant current the flux of drug should remain essentially constant until the last molecule is delivered.

Turning to the rejection based on Haak et al, U.S. Patent No. 5,203,768, alone or in view of the '894 patent, the Examiner has based the rejection on an erroneous interpretation of the claims. The claims recite that the defined concentration of the fentanyl

salt is maintained throughout the total iontophoretic delivery period. As supported by the specification (which must interpret the claims), it is clear that this does not include the intermittent stoppage of a device such as described in Haak et al. Instead, the claims refer to the period when the total delivery is stopped, such as when one removes the device which can result when one reaches the last programmed dosage. As noted by Dr. Phipps, Haak et al does not disclose or teach this aspect of the present invention and certainly does not recognize that the total delivery should be terminated when the concentration is above the defined level in order obtain a constant flux as recited in the claims. Indeed, the present invention actually proceeds against conventional wisdom of using low residual concentrations of fentanyl for the safety reasons noted in Dr. Phipps previous Declaration.

As to the combination of Haak et al with the '894 patent, Dr. Phipps has stated that such combination also would not result in the present invention. As noted above, a proper understanding of what the '894 patent teaches would lead those in the art to using a low concentration of fentanyl salt in view of the teaching that steady state delivery can be obtained at very low concentrations and in light of the potency of fentanyl. Dr. Phipps has thus concluded that it is entirely unexpected that he has found that the defined high concentration of fentanyl salt is necessary in order to obtain the iontophoretic flux set forth in the claims.

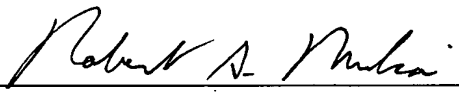
Applicant again notes that when the full scope of the knowledge in the art is considered, as one must do, it is clear that those in the art would be led to a low residual concentration of fentanyl in a used fentanyl-administering iontophoretic delivery device.

The present invention is contrary to this understanding and leads to the conclusion that the present invention is patentable over the teachings of the prior, similar to the conclusion reached in In re Hedges et al, 228 USPQ 685 (Fed. Cir. 1986) where the court reversed a prior art rejection stating in part that the fact that the inventor proceeded contrary to accepted wisdom is strong evidence of unobviousness.

Accordingly, based on the claims and evidence of record, applicants respectfully submit that the present invention is patentable in all regards and therefore request entry of the instant response and reconsideration and allowance of the present application.

Respectfully submitted,

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